Remarks

No new matter has been added by way of this amendment. Following entry of this amendment, claims 20-29, 38, 39, 49-58, 60-73 are pending in the application. Applicants have amended the specification to correct typographical errors. Specifically, Applicants have corrected the specification to remove the reference to a bacterial host. The cDNA clone of the invention was not deposited in a bacterial host, but as a plasmid. A copy of the ATCC Deposit Receipt is attached hereto as evidence thereof. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Examiner Interview

Applicants thank Examiner Kuntz for the courteous and helpful personal interview extended to Applicants' representative, Eric Steffe, on June 26, 2002.

Introduction: IL-1R AcM and IL-1R

The soluble interleukin-1 receptor accessory molecule (IL-1R AcM) protein of the invention plays an important role in IL-1 receptor biology. By way of background, the IL-1 family comprises three members: IL-1α, IL-1β and the IL-1 receptor antagonist, IL-1ra. (Specification at page 2, lines 1-4 and 15-18.) These ligands bind to two distinct and

separate receptors: the Type I and Type II IL-1 receptors (IL-1Rs). *Id.* The agonists IL-1α and IL-1β bind to the extracellular domains of both receptors, although with different affinities. *Id.* IL-1ra is a naturally-occurring IL-1 inhibitor.

The specification further teaches, *inter alia*, at page 33, lines 7-13, that the soluble IL-1R AcM protein of the present invention is involved in IL-1 activity and forms a complex with the type I IL-1R allowing IL-1β to bind with higher affinity to the Type I IL-1R. The low affinity site corresponds to the Type I IL-1R alone, while the higher affinity site represents a complex of the Type I IL-1R with the IL-1R AcM. Thus, IL-1R AcM plays a major role in IL-1 signal transduction events by, *inter alia*, forming a high affinity IL-1R binding state.

Clinical and experimental evidence suggests that shock, arthritis, osteoporosis, colitis, leukemia, diabetes, wasting and atherosclerosis are mediated, in part, by IL-1. Inhibition of this cytokine has been a strategy for studying disease and for new drug development. For example, the naturally occurring IL-1 receptor antagonist, IL-1ra, blocks binding of the IL-1 ligand to its receptors. IL-1ra reduces the severity of sepsis, colitis, arthritis and diabetes in animals and is presently being tested in humans with arthritis, shock and myelogenous leukemia. Dinarello *et al.*, *Immunol. Today 12*:404-410 (1991). *See also* specification at page 42, line 17, to page 43, line 9. In addition to IL-1ra, IL-1R-blocking antibodies or soluble IL-1R fragments have been used to specifically inhibit IL-1 activity. *See* Dinarello *et al.*, *Int. J. Clin. Lab. Res. 24*:61-79 (1994).

Given that the IL-1 ligand has many diverse effects on immunologic and inflammatory processes and that the IL-1 ligand elicits a wide variety of effects in hematic and nonhematic cells, IL-1R AcM is thus useful, *inter alia*, to identify or generate

modulators (agonists and antagonists) of IL-1 activity. *See* specification, at page 33, lines 13-18. Various utilities for IL-1R AcM are discussed in further detail below.

Human IL-1R AcM and Mouse IL-1R AcM

Greenfeder *et al.*, *J. Biol. Chem. 270*:13757-13765 (1995) (copy submitted as document AS3 in the IDS filed on November 26, 1997), disclose the cloning and characterization of the murine IL-1 receptor accessory protein (muIL-1R AcP). The IL-1R AcM protein of the invention is about 94% similar and 85% identical to muIL-1R AcP. *See* specification at pages 8-9 and Figure 2A. Greenfeder *et al.* indicate via ligand binding and cross-linking studies that the muIL-1R AcP is directly involved in IL-1 ligand activity and that it forms an essential component of the IL-1R complex. In the presence of muIL-1R AcP, IL-1β binds with higher affinity to the murine Type I IL-1R. *Id.* Thus, the muIL-1R AcP increases the binding affinity of the Type I IL-1R for the IL-1β ligand. The results reported by Greenfeder *et al.* further strengthen Applicants' assertion that IL-1R AcM forms an essential component of the IL-1R complex and increases the binding affinity of the Type I IL-1R for the IL-1β ligand.

IL-1R AcM Has Specific, Substantial and Credible Utility

Diagnostic Utility

Agonists and Antagonists

Since IL-1R AcM forms an essential component of the IL-1R complex and increases the binding affinity of the Type I IL-1R for IL-1β, IL-1R AcM is useful, *inter alia*, for identifying IL-1 receptor agonists and antagonists. Stable cell lines that are established by

simultaneous cotransfection of two expression vectors, and control cell lines which express only IL-1R or IL-1R AcM can be used in screening assays to identify potential agonists and antagonists for IL-1.

For example, to identify IL-1 signal transduction agonists, a cell line should express an excess amount of IL-1R AcM protein relative to IL-1R. The presence of the IL-1R AcM protein of the present invention in the cell line used for agonist screening ensures that the IL-1R is in a high affinity binding state. Cell lines bearing only IL-1R AcM protein will not bind IL-1β and cell lines bearing only IL-R bind IL-1β with low affinity (*i.e.*, on the order of K_D 1.0-3.3nM). A CHO-IL-1R/AcM cell line, bearing both the IL-1R and IL-1R AcM results in the IL-1R having a higher affinity binding site (*i.e.*, on the order of K_D 0.02-0.8 nM). Thus, one can monitor the relative binding affinity of the candidate agonist relative to the IL-1β. *See* specification at page 34, lines7-15.

IL-1R AcM is also useful for identifying IL-1 signal transduction antagonists. Greenfeder *et al.* teach that the antagonist IL-1ra prevents or disrupts formation of a complex between muIL-1R and muIL-1R AcP. Thus, a screening method for identifying other antagonists of signal transduction would involve expressing IL-1R and IL-1R AcM or an IL-1R AcM fragment, wherein IL-1R and IL-1R AcM or IL-1R and the IL-1R AcM fragment form a complex, administering a candidate antagonist and determining whether the candidate antagonist disrupts or prevents formation of a complex between IL-1R and IL-1R AcM or IL-1R and a IL-1R AcM fragment.

Antibodies

In addition, IL-1R AcM is also useful for generating antibodies. These antibodies are useful, *inter alia*, for immunoprecipitating cross-linked complexes for the antagonist screening assay as well as showing that stable cell lines are in fact expressing the Type I IL-1R and IL-1R AcM proteins. *See* specification at page 36, lines 21-27. Methods for obtaining IL-1R AcM antibodies are set forth in the specification, *inter alia*, at pages 36-38.

Therapeutic Uses of IL-1R AcM

Antibody Therapy

In view of the wide range of roles that the IL-1 ligand plays in physiologic and pathologic processes (*see* specification at pages 42-43), regulating the action of the IL-1 ligand by abrogating signal transduction from the IL-1 binding complex is useful for therapeutic purposes. For example, in animal studies, reduction of IL-1R activity significantly reduced the severity of diseases, including those associated with infections, inflammation and metabolic disturbances. *Id.* at 43. In addition, studies with human subjects have also demonstrated that reduction of IL-1R activity is effective where the severity of disease is high. For example, dramatic results have been seen in patients with septic shock. In another clinical trial, rheumatoid arthritis patients treated with IL-1ra, in addition to other non-steroidal anti-inflammatory drugs, had a significant reduction in the number and severity of painful and swollen joints. These results demonstrate an improvement in the clinical disease of these patients. *Id.* at 44.

Given that IL-1R AcM is involved in IL-1 signal transduction, antibodies directed against IL-1R AcM are expected to behave as agonists or antagonists of IL-1 activity. For

example, an antibody directed against the murine IL-1R accessory protein blocked the binding of IL-1β to murine type I IL-1R (Greenfeder *et al.*, *J. Biol. Chem. 270*:13757-13765 (1995)). Thus, antibodies directed against the IL-1R AcM of the present invention that abrogate IL-1 activity can be used therapeutically to reduce the severity of diseases associated with IL-1. Similarly, IL-1R AcM fragments or derivatives that abrogate IL-1 activity can also be used therapeutically to reduce the severity of diseases associated with IL-1.

In summary, IL-1R AcM plays a major role in IL-1 signal transduction events and forms a complex with the type I IL-1R allowing IL-1β to bind with higher affinity to the Type I IL-1R. Antibodies directed against IL-1R AcM are expected to behave as agonists or antagonists of IL-1 activity. In addition, IL-1R AcM is useful, *inter alia*, for identifying IL-1 receptor agonists and antagonists. Thus, IL-1R AcM has specific, substantial and credible utility.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite

prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Gaby L. Longsworth

Gaby L. Longsworth, Ph.D.
Agent for Applicants
Registration No. 47,756

Date: July 29, 2002

1100 New York Avenue, N.W.
Suite 600
Washington, D.C. 20005
(202) 371-2600

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Version with markings to show changes made

In the Specification

The first paragraph at page 3 was substituted with the following paragraph:

It has been assumed that the functional Type I IL-1R is a single chain receptor (Curtis, B.M., *et al., Proc. Natl. Acad. Sci. USA, 86*:3045-3049 (1989)). However, affinity cross-linking of IL-1 to cells expressing natural IL-1 receptor has yielded complex patterns of cross-linked proteins (Dower, *et al., Cellular and Molecular Mechanisms of Inflammation,* pp. 137-172, Academic Press, Orlando FL (1990); Dinarello, *et al., Immunol. Today,* 10: 49-51 (1989)). These cross-linking studies detect molecular mass complexes consistent with both the Type I and Type II IL-1Rs cross-linked to IL-1. In addition, in some studies, higher molecular mass complexes (>200 kD) are apparent (Kupper, T.S., *et al., J. Clin. Invest. 82*:1787-1792 (1988); Dinarello, C.A., *et al., Immunol. Today 10*:49-51 (1989); Solari, R., *Cytokine 2*:21-28 (1990); Mancilla, J., *et al., Lymph. Cytokine Res. 11*:197-205 (1992)). Some reports have interpreted these higher molecular mass complexes to be [dimmers] <u>dimers</u> of receptor-ligand complexes. Others have concluded that these high molecular mass complexes maybe indicative of a multi-subunit IL-1 receptor complex.

The paragraph beginning on page 5, line 11, was substituted with the following paragraph:

The present invention provides isolated nucleic acid molecules comprising a polynucleotide encoding the soluble IL-1R AcM polypeptide having the amino acid sequence [is] as shown in Figure 1 [[SEQ ID NO:2]] (SEQ ID NO:2) or the amino acid sequence encoded by the cDNA clone deposited [in a bacterial host] as ATCC Deposit Number 97666 on July 25, 1996. The nucleotide sequence determined by sequencing the deposited IL-1R AcM clone, which is shown in Figure 1 [[SEQ ID NO:1]] (SEQ ID NO:1), contains an open reading frame encoding a polypeptide of 356 amino acid residues, including an initiation codon at positions 303-305, with a leader sequence of about 17 amino acid residues, and a predicted molecular weight of about 42 kDa. The amino acid sequence of the mature IL-1R AcM protein is amino acid residues 18-356 shown in Figure 1 or 1-339 shown in SEQ ID NO:2.

The paragraph beginning on page 9, line 7, was substituted with the following paragraph:

The present invention also provides the mature form(s) of the soluble IL-1R AcM protein of the present invention. According to the signal hypothesis, proteins secreted by mammalian cells have a signal or secretory leader sequence which is cleaved from the mature protein once export of the growing protein chain across the rough endoplasmic reticulum has been initiated. Most mammalian cells and even insect cells cleave secreted proteins with the same specificity. However, in some cases, cleavage of a secreted protein is not entirely uniform, which results in two or more mature species on the protein. Further, it has long been known that the cleavage specificity of a secreted protein is ultimately

determined by the primary structure of the complete protein, that is, it is inherent in the amino acid sequence of the polypeptide. Therefore, the present invention provides a nucleotide sequence encoding the mature soluble IL-1R AcM polypeptides having the amino acid sequence encoded by the cDNA clone [contained in the host] identified as ATCC Deposit No. 97666 and as shown in SEQ ID NO:2. By the mature soluble IL-1R AcM protein having the amino acid sequence encoded by the cDNA clone [contained in the host] identified as ATCC Deposit 97666 is meant the mature form(s) of the soluble IL-1R AcM protein produced by expression in a mammalian cell (e.g., COS cells, as described below) of the complete open reading frame encoded by the human DNA sequence of the clone contained in the vector [in the deposited host]. As indicated below, the mature soluble IL-1R AcM having the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. 97666 may or may not differ from the predicted "mature" soluble IL-1R AcM protein shown in SEQ ID NO:2 (amino acids from about 1 to about 339) depending on the accuracy of the predicted cleavage site based on computer analysis.

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PF307

BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF
THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT ISSUED PURSUANT TO RULE 7.3
AND VIABILITY STATEMENT ISSUED PURSUANT TO RULE 10.2

To: (Name and Address of Depositor or Attorney)

Human Genome Sciences, Inc.
Attn: Robert H. Benson
9410 Key West Avenue
Rockville, MD 20850

Deposited on Behalf of: Human Genome Sciences, Inc.

Identification Reference by Depositor:

DNA Plasmid 1450621

ATCC Designation

97666

The deposit was accompanied by: ___ a scientific description _ a proposed taxonomic description indicated above.

The deposit was received July 25, 1996 by this International Depository Authority and has been accepted.

AT YOUR REQUEST: X We will inform you of requests for the strain for 30 years.

The strain will be made available if a patent office signatory to the Budapest Treaty certifies one's right to receive, or if a U.S. Patent is issued citing the strain, and ATCC is instructed by the United States Patent & Trademark Office or the depositor to release said strain.

If the culture should die or be destroyed during the effective term of the deposit, it shall be your responsibility to replace it with living culture of the same.

The strain will be maintained for a period of at least 30 years from date of deposit, or five years after the most recent request for a sample, whichever is longer. The United States and many other countries are signatory to the Budapest Treaty.

The viability of the culture cited above was tested August 1, 1996. On that date, the culture was viable.

International Depository Authority: American Type Culture Collection, Rockville, Md. 20852 USA

Signature of person having authority to represent ATCC:

Barbara M. Hailey, Administrator, Patent Depository

Date: August 2, 1996

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